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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/511,130

08/15/2005

Bernard Connolly

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EXAMINER

HUTSON, RICHARD G

ART UNIT

PAPER NUMBER

1652

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/511,130	Applicant(s) CONNOLLY ET AL.	
	Examiner Richard G. Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/27/2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-6,9,10,23,26 and 27 is/are pending in the application.
- 4a) Of the above claim(s) 23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-6,9,10, 26 and 27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10/13/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>8/15/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants submitted sequence listing 8/27/2009, is acknowledged. Applicant's cancellation of claims 2, 7-8, 11-22, 24 and 25, amendment of claim 6, in the paper of 6/19/2009, is acknowledged. Claims 1, 3-6, 9, 10, 23, 26 and 27 are still at issue and are present for examination.

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1, 3-6, 9, 10, 23, 26 and 27 to a variant archaeal DNA polymerase, in the paper of 2/11/2009, and the election without traverse of *Pyrococcus furiosus* (Pfu-Pol) from Species Group I and those modifications corresponding to V93 of SEQ ID NO:2 from Species Group 2, in the paper of 6/19/2009, is acknowledged.

It is noted that both of the previous restriction requirements were just that, restriction requirements, not species election requirements.

Accordingly, claim 23 as well as those mutant positions not V93 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the

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list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosure statement, filed on 8/15/2009, is acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth: The following portions of the specification list sequences which appear to meet the definition for a amino acid sequence, but do not have an associated SEQ ID No: Figure 1 and 2 comprise sequence which require a sequence identifier either in the figure or in the description of the figure..

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 9, 10, 23, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-6, 9, 10, 23, 26 and 27 are directed to all possible variant archaeal DNA polymerases having a modified amino acid sequence of a wild-type amino acid sequence, the modified sequence being in the amino-terminal amino acids that comprise a uracil-binding pocket in the wild-type polymerase whereby the variant polymerase has reduced affinity for uracil than the wild-type polymerase. It is noted that applicants claimed variant DNA polymerases while referring to variations of wild-type archaeal DNA polymerase comprise no structural limitations outside of those positions of the polymerase which are modified. Thus the claimed variant archaeal DNA polymerase lacks sufficient structure to adequately describe the those variant archaeal polymerases encompassed by the claims. The specification, however, only provides a single representative species of variant archaeal DNA polymerase comprising the amino acid sequence of SEQ ID NO:2 with a substitution at position V93, encompassed by the broadly claimed genus. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these variant polymerases by any identifying structural characteristics or properties other than the activities recited in claims 1, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms

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that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 3-6, 9, 10, 23, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a variant archaeal DNA polymerase comprising the amino acid sequence of SEQ ID NO:2 with a substitution at position V93, does not reasonably provide enablement for any variant archaeal DNA polymerases having a modified amino acid sequence of a wild-type amino acid sequence, the modified sequence being in the amino-terminal amino acids that comprise a uracil-binding pocket in the wild-type polymerase whereby the variant polymerase has reduced affinity for uracil than the wild-type polymerase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

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the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 3-6, 9, 10, 23, 26 and 27 are so broad as to encompass any variant archaeal DNA polymerase having a modified amino acid sequence of a wild-type amino acid sequence, the modified sequence being in the amino-terminal amino acids that comprise a uracil-binding pocket in the wild-type polymerase whereby the variant polymerase has reduced affinity for uracil than the wild-type polymerase. As discussed above, it is noted that applicants claimed variant DNA polymerase(s), while referring to variations of a wild-type archaeal DNA polymerase, comprise no structural limitations outside of those positions of the polymerase which are modified. Thus the claimed variant archaeal DNA polymerase lacks sufficient structure to enable the breadth of the genus of those variant archaeal polymerases encompassed by the claims. Thus the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variant polymerases broadly encompassed by the claims. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed variant outside of the specific mutation positions of the polymerase. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the

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proteins' structure relates to its function. However, in this case the disclosure is limited to that variant archael DNA polymerase comprising the amino acid sequence of SEQ ID NO:2 with a substitution at position V93.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any variant archael DNA polymerase having a modified amino acid sequence of a wild-type amino acid sequence, the modified sequence being in the amino-terminal amino acids that comprise a uracil-binding pocket in the wild-type polymerase whereby the variant polymerase has reduced affinity for uracil than the wild-type polymerase because the specification does not establish: (A) regions of the protein structure which may be modified without effecting polymerase activity in combination with reduced uracil affinity; (B) the general tolerance of archael DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of an archael DNA polymerase with an expectation of obtaining the desired biological function; and

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(D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which modifications would be acceptable to retain the polymerase activity while reducing the uracil affinity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those variant DNA polymerases of the claimed genus having polymerase activity while reducing the uracil affinity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any variant archaeal DNA polymerase having a reduced affinity for uracil compared to the wild-type polymerase. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those variant DNA polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rg
12/4/2009

/Richard G Hutson/
Primary Examiner, Art Unit 1652